Amendments to the Specification:

Please amend the specification as follows:

Please delete the title, lines 1-2 on page 1, and replace it with the following title:

THREE-DIMENSIONAL STRUCTURE OF POLYKETIDE SYNTHASES

Please edit the paragraph on page 9, line 5 to page 9, line as follows:

"Mutant" or "mutated synthase" refers to a polyketide synthase polypeptide, having the three-dimensional coordinates as set forth in Protein Data Bank (PDB) Accession No. 1BI5 (~~the content of which is incorporated herein by reference in its entirety~~ **Table 5**), and having R-groups on each α-carbon other than the prescribed arrangements of R-groups associated with each α-carbon of a known isolated polyketide synthase (Accession No. 1BI5, **Table 5**). Examples of mutant or mutated synthase polypeptides include those having Protein Data Base Accession No. 1D6F, ~~1K6I~~, **1D6I** and 1D6H (~~the content of which are incorporated herein by reference in their entirety~~ **Tables 6-8, respectively**). ~~Access to the foregoing information in the Protein Data Bank can be found at www.resb.org.~~

Please edit the paragraph on page 15, line 8 to page 16, line 21 as follows:

A "comparison window", as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of from 20 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequence for comparison are well-known in the art. Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the

local homology algorithm of Smith & Waterman, Adv. Appl. Math. 2:482, 1981, by the homology alignment algorithm of Needleman & Wunsch, J. Mol. Biol. 48:443,1970, by the search for similarity method of Person & Lipman, Proc. Nat'1. Acad. Sci. USA 85:2444, 1988, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection. Other algorithms for determining homology or identity include, for example, in addition to a BLAST program (Basic Local Alignment Search Tool at the National Center for Biological Information), ALIGN, AMAS (Analysis of Multiply Aligned Sequences), AMPS (Protein Multiple Sequence Alignment), ASSET (Aligned Segment Statistical Evaluation Tool), BANDS, BESTSCOR, BIOSCAN (Biological Sequence Comparative Analysis Node), BLIMPS (BLocks IMProved Searcher), FASTA, Intervals & Points, BMB, CLUSTAL V, CLUSTAL W, CONSENSUS, LCONSENSUS, WCONSENSUS, Smith-Waterman algorithm, DARWIN, Las Vegas algorithm, FNAT (Forced Nucleotide Alignment Tool), Framealign, Framesearch, DYNAMIC, FILTER, FSAP (Fristensky Sequence Analysis Package), GAP (Global Alignment Program), GENAL, GIBBS, GenQuest, ISSC (Sensitive Sequence Comparison), LALIGN (Local Sequence Alignment), LCP (Local Content Program), MACAW (Multiple Alignment Construction & Analysis Workbench), MAP (Multiple Alignment Program), MBLKP, MBLKN, PIMA (Pattern-Induced Multisequence Alignment), SAGA (Sequence Alignment by Genetic Algorithm) and WHAT-IF. Such alignment programs can also be used to screen genome databases to identify polynucleotide sequences having substantially identical sequences. A number of genome databases are available, for example, a substantial portion of the human genome is available as part of the Human Genome Sequencing Project (J. Roach,-**available on the world wide web at** ~~**http:**~~//weber.u.Washington.edu/~roach/human_genome_progress_2. html) (Gibbs, 1995). At least twenty-one other genomes have already been sequenced, including, for example, *M. genitalium* (Fraser *et al.*, 1995), *M. jannaschii* (Bult *et al.*, 1996), *H. influenzae* (Fleischmann *et al.*, 1995), *E. coli* (Blattner *et al.*, 1997), and yeast (*S. cerevisiae*) (Mewes *et al.*, 1997), and *D.*

melanogaster (Adams *et al.*, 2000). Significant progress has also been made in sequencing the genomes of model organism, such as mouse, *C. elegans*, and *Arabadopsis sp.* Several databases containing genomic information annotated with some functional information are maintained by different organizations, and are accessible ~~via the internet~~ **on the world wide web**, for example, **at** ~~**http://www.**~~tigr.org/tdb; ~~**http://www.**~~genetics.wisc.edu; ~~**http://**~~genome-www.stanford.edu/-ball; ~~**http://**~~hivweb.lanl.gov; ~~**http://www.**~~ncbi.nlm.nih.gov; ~~**http://www.**~~ebi.ac.uk; ~~**http://**~~Pasteur.fr/other/biology; and ~~**http://www.**~~genome.wi.mit.edu.

Please edit the paragraph on page 16, line 22 to page 17, line 16 as follows:

One example of a useful algorithm is BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al.*, Nuc. Acids Res. 25: 3389-3402, 1977, and Altschul *et al.*, J. Mol. Biol. 215: 403-410,1990, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (**available on the world wide web at** ~~**http://www.**~~ncbi.nlm.nih.gov). This algorithm involves first identifying high scoring sequence pairs(HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul *et al.*, *supra*). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters

W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectations (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff & Henikoff, Proc. Natl. Acad. Sci. USA 89: 10915, 1989) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

Please edit the paragraph on page 17, line 17 to page 17, line 25 as follows:

The BLAST programs identify homologous sequences by identifying similar segments, which are referred to herein as "high-scoring segment pairs," between a query amino or nucleic acid sequence and a test sequence which is preferably obtained from a protein or nucleic acid sequence database. High-scoring segment pairs are preferably identified (*i.e.*, aligned) by means of a scoring matrix, many of which are known in the art. Preferably, the scoring matrix used is the BLOSUM62 matrix (Gonnet *et al.*, Science 256: 1443-1445,1992; Henikoff and Henikoff, Proteins 17:49-61,1993). Less preferably, the PAM or PAM250 matrices may also be used (see, *e.g.*, Schwartz and Dayhoff, eds., 1978, *Matrices for Detecting DistanceRelationships : Atlas of Protein Sequence and Structure*, Washington: National Biomedical Research Foundation). BLAST programs are accessible through the U. S. National Library of Medicine, *e.g.*, **on the world wide web** at ~~www.~~ncbi.nlm.nih.gov.

Please edit the paragraph on page 175, line 3 to page 173, line 13 as follows, wherein the paragraph title "Mutagenesis, expression, and purification" below is not newly added text but merely reflects underlining in the original specification:

Mutagenesis, expression, and purification. Alfalfa CHS2 cDNA (Junghans, H., *et al.*, Plant Mol. Biol. 22:239-253,1993) was subcloned into pHIS8 plasmid vector derived from pET-28a (+) (Novagen). PCR-based mutagenesis using the QUIKCHANGE™ system (Stratagene) generated the various mutants including $C_{164}S$, $C_{164}D$, $H_{303}A$, $H_{303}Q$, $H_{303}D$, $H_{303}T$, $N_{336}A$, $N_{336}D$, $N_{336}Q$, $N_{336}H$, $F_{215}S$, $F_{215}Y$ and $F_{215}W$. N-teminal His8-tagged CHS was expressed in BL21 (DE3) *E. coli* cells. Cells were harvested and lysed by sonication. His-tagged CHS was purified from bacterial sonicates using a NI-NTA (Qiagen) column. Thrombin digest removed the His-tag and the protein was passed over another NI-NTA column and a benzamidine SEPHAROSE® (Pharmacia) column. The final purification step used a SUPERDEX™ 200 16/60 (Pharmacia) column.

Please add the following paragraphs after the last line of the specification at page 193:

Table 5. PDB Accession No. 1BI5. The content of Table 5 is hereby incorporated by reference under 37 C.F.R. § 1.52(e)(1)(iii) to file "Table5.txt" of CD-R disk "Tab-5-8", created September 6, 2005, with size 619,981 bytes.

Table 6. PDB Accession No. 1D6F. The content of Table 6 is hereby incorporated by reference under 37 C.F.R. § 1.52(e)(1)(iii) to file "Table6.txt" of CD-R disk "Tab-5-8", created September 6, 2005, with size 313,711 bytes.

Table 7. PDB Accession No. 1D6I. The content of Table 7 is hereby incorporated by reference under 37 C.F.R. § 1.52(e)(1)(iii) to file "Table7.txt" of CD-R disk "Tab-5-8", created September 6, 2005, with size 557,743 bytes.

Table 8. PDB Accession No. 1D6H. The content of Table 8 is hereby incorporated by reference under 37 C.F.R. § 1.52(e)(1)(iii) to file "Table8.txt" of CD-R disk "Tab-5-8", created September 6, 2005, with size 302,313 bytes.